HYPOCHLOREMIA*

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THE importance of the various blood electrolytes in relation to the life and health of animals and of man is now well recognized. Changes in the normal concentration of certain ions, or fluctuations in the balance between others, are associated with certain morbid conditions occurring spontaneously or produced experimentally. Following surgical operations, during which ether is used as the anesthetic, there occur definite changes in the calcium-potassium ratio of the blood. These are accompanied by a period of postoperative lethargy, and a marked tissue thirst, (Reuter and Andrews [1]). The lowering of the blood calcium in parathyroid tetany is now a matter of common observation, likewise its increase subsequent to the administration of Collip's hormone. In cretinism, the blood iodide is low. It is similarly lowered in individuals with non-toxic nodular goiters (de Quervain and Smith [3]). Clinical blood-chemical studies by Lunde [6] seem to have demonstrated the significance of the blood iodide in relation to the preoperative iodine treatment of exophthalmic goiter and the results of the subsequent thyroidectomy.

The chlorides of the blood, since they are the more readily determined by various analytical methods, have been particularly studied. The hypochloremia of upper intestinal obstruction has been frequently confirmed. A similar lowering of the blood chlorides is associated with the fatal effect of the total loss of gastric juice (Dragstedt and Ellis [4]). Orr and Haden [5] have recently reported that hypochloremia also occurs in dogs with fatal experimental peritonitis. We have observed a marked hypochloremia accompanying a strangulated hernia of omentum.[6] The blood chloride is low despite the blood concentration of the so-called toxemia following extensive superficial burns (Underhill et al.[7]). The symptoms of heat cramps, called also miner's cramp, stoker's cramp, or fireman's cramp, are initiated by a marked loss of perspired chlorides and are relieved by giving salt solutions. In view of these and other clinical findings, it appeared that the

associated hypochloremia was possibly of more than subordinate importance. As a consequence, we have produced and studied it, as well as other changes in the blood chemistry, by the method of peritoneal dialysis.

Various crystalloids may be readily dialyzed away from the circulating blood through celloidin tubes inserted in the course of the blood stream. This process, called *vividiffusion*, was devised by Abel, Rowntree and Turner.[8] Dialysis also readily occurs through the serous membranes lining the body cavities.[9] [10] Cohnheim [11] found that chlorides soon appear in glucose solutions injected intraperitoneally in rabbits. This is likewise true when varying concentrations of saccharose are employed.[12] When distilled water is injected intraperitoneally, a higher per cent of chlorides, up to 0.63 per cent, calculated as sodium chloride, is deviated from the blood stream and the blood chloride falls.[13] The intraperitoneal fluid soon becomes isosmotic and obtains up to 1.5 per cent of albuminous substance. Achloride electrolytes, as well as organic crystalloids, are likewise dialyzed from the blood stream. Consequently, it has been possible to lower the blood chloride experimentally by perfusing distilled water, or various chloride-free solutions, through the peritoneal cavity.[14]

COMMENT ON EXPERIMENTS WITH RABBITS

Healthy male rabbits, weighing between 2 and 2.5 kilos, were used throughout the experiments to be described. They were carefully prepared and given ample food and water, according to methods which have been outlined elsewhere.[12] After binding them to a padded animal board, a soft rubber catheter (a demeure) was introduced into the bladder. They were then lightly covered and kept warm by overhanging lamps. Under local anesthesia a steel trocar-inlet was inserted through the upper left abdominal wall, and by means of a lower abdominal incision a large, multiply perforated rubber tube was placed free in the right lateral peritoneal cavity, posterior to the intestines. In this manner extensive perfusion was assured. The perfusion fluid employed was maintained at body temperature by passage through a heated coil and the perfusion rate was kept uniformly at 500 cubic centimeters per hour. Blood was collected from the peripheral veins, or at death from the right heart.

In fifteen experiments distilled water alone was perfused through the peritoneal cavity. Within an hour there is an increase in the respiratory rate and fibrillary twitchings appear, usually in

the muscles of the abdomen or extremities. These become more generalized, then coarser and more severe, and are followed by clonic and eventually tonic convulsions of increasing severity. Spasmodic contractions of the diaphragm also appear, and the animals die in from two to five hours after the beginning of the perfusion, usually after a severe convulsion.

During an experiment chloride is dialyzed from the blood and tissues. At the end there is often a marked lowering of the blood chloride. This hypochloremia may reach as low as 118 milligrams per 100 cubic centimeters of whole blood. The carbon dioxide combining power of the plasma falls and may become as low as ten volumes per cent. There is a moderate rise in the non-protein nitrogen, and a slight elevation of the urea concentration. The secretion of urine diminishes soon after the establishment of perfusion, and finally completely ceases. This subsequent anuria is a constant finding. Abel [8] has also noted that little or no urine was secreted during his vividiffusion experiments.

The development of the symptoms and the subsequent lethal effect are not associated with an hypoglycemia, since the terminal blood sugar varied between 242 and 284 milligrams per 100 cubic centimeters; in fact, it was higher than that found preceding the commencement of the perfusion. The possibility of hypoglycemia, however, was considered. To answer the question of hypoglycemic convulsions more precisely, particularly in regard to a possible depletion of the sugar reserves by dialysis, in fifteen experiments 0.12 per cent glucose, about the concentration normally present in the rabbit's blood, was added to the perfusion water. There was no appreciable effect upon the development of the usual symptoms or the ordinarily fatal outcome. The usual hypochloremia developed, as well as changes in the blood chemistry similar to those following the perfusion of distilled water alone, with this particular exception, that the terminal blood sugar became even higher; in one instance 320 milligrams per 100 cubic centimeters. There was little or no secretion of urine, and in most instances an anuria. In all thirty experiments definite hemolysis was observed. Demineralization occurred, to the extent of the diffusibility of the dialyzable electrolytes. There was also a loss of albuminous substance, washed out by the perfusing fluid. Further experiments were then devised in an attempt to evaluate these factors in so far as they might be causes of the development of the symptoms and of the ordinarily fatal outcome.

To overcome the effects of demineralization of the blood due to the dialysis of blood sodium, potassium, calcium and chloride ions into the perfusing distilled water, Ringer's solution with glucose (NaCl 0.7 per cent, KCl 0.03 per cent, $CaCl_2$ 0.025 per cent, glucose 0.143 per cent) was substituted and was perfused through the peritoneal

cavity by the same methods. During the course of these experiments the animals showed no evidence of increased nervous irritability. There were no muscular twitchings, tremors or convulsions. The animals were alive and in good condition when perfusion was terminated at the end of eight or nine hours. The blood chloride at the end of an experiment was slightly higher than before the perfusion began. During these experiments there was a continuous secretion of urine. Usually this was at a normal even rate; however, in one animal a moderate diuresis ensued during the second hour of perfusion. There was some hemolysis, and albuminous substance was washed out by the perfusion fluid.

The relative importance of the individual ions was then considered. The potassium and calcium were first withdrawn from the perfusion fluid and 0.9 per cent pure sodium chloride substituted in place of Ringer's solution. In half the experiments, 0.12 per cent pure glucose was added. The sodium chloride used in making this solution, and in subsequent experiments, was the purest obtainable (Kahlbaum's), and contained no other ions. Four animals were alive and in good condition when perfusion was terminated at the end of 8, 8, 9, and 10 hours respectively. One animal, perfused with saline containing glucose, showed definite muscular twitchings and contractions. The others were quiet during the experiments. All four showed increased irritability at the end. During all experiments there was a continuous secretion of urine, and in one animal a moderate diuresis occurred. The whole blood chlorides at the end were higher than previous to the commencement of perfusion, averaging 546 milligrams per 100 cubic centimeters. The blood sugars were higher in the experiments in which glucose was used, averaging 191 milligrams per 100 cubic centimeters. There was a fall in the carbon dioxide combining power of the plasma, and a slight decrease in the N. P. N. and urea concentrations. The serum calcium fell, in one experiment, to 2.9 milligrams per 100 cubic centimeters. This animal showed no muscular twitchings, tremors or contractions and was quiet during the latter part of the perfusion. There was thus a *hypocalcemia* without tetany. There was a slight hemolysis.

An isotonic solution without electrolytes, 4.2 per cent pure glucose, was then used. Chloride is readily dialyzed from the blood into intraperitoneal glucose solutions.[11] In these experiments, increased respirations, muscular twitchings, tremors, and convulsions ensued. The picture, however, was not typical of the symptoms ordinarily following the perfusion of distilled water alone. The animals died in from 2½ to 7 hours. The terminal blood was hypochloremic, 136 milligrams per 100 cubic centimeters. There was an enormous rise in the blood sugar. Perfusion of an isotonic solution containing 0.45 per cent sodium chloride and 2.1 per cent glucose had no such lethal effect and the animal was alive when the

experiment was terminated at the end of 9½ hours. The terminal blood in this animal showed a slight rise in the chloride content and an enormous increase in the sugar concentration. Another animal was alive when the perfusion of a hypertonic solution, 0.9 per cent sodium chloride and 2.1 per cent glucose, was terminated at the end of eight hours.

Ringer's solution with glucose, but *without sodium chloride*, (KCl 0.03 per cent, $CaCl_2$ 0.025 per cent, glucose 0.143 per cent) was then used. In this manner adequate amounts of calcium and potassium were supplied during the perfusion, but no sodium and inadequate chloride, since by dialysis chlorides enter this hypotonic fluid from the blood stream. Increased respirations, muscular twitchings and convulsions ensued as the perfusion continued, and the animals died in between five and six hours. The hypochloremia which developed was not so marked as in the distilled water experiments, 181 milligrams per 100 cubic centimeters. The secretion of the urine diminished and then ceased. There was a definite hemolysis and a loss of albuminous substance in the perfusion fluid.

CONCLUSIONS

A consideration of the preceding experiments led to the hypothesis that the loss of chloride was an important factor in the development of the characteristic symptoms and the ordinarily fatal outcome following the perfusion of distilled water through the peritoneal cavity. Whether this might be due to the specific deficiency, or to some associated change, such as a lowering of the blood osmotic concentration, was not clear. The hypothesis was tested experimentally by supplying an adequate amount of pure sodium chloride alone to the blood stream throughout the transperitoneal perfusion with distilled water. This was accomplished by timed intravenous injections by means of the Woodyatt pump.

After a number of unsuccessful attempts, it was found best to inject a 2.5 per cent solution of pure sodium chloride at the rate of one cubic centimeter per minute into one of the cannulated jugular veins. When too concentrated solutions are used, for example, nine per cent, thrombosis occurs locally and in one animal was followed by pulmonary embolism. If the solution is too dilute, sodium chloride is not supplied as rapidly as it is dialyzed away; also too much water ·must be simultaneously injected.

When distilled water or distilled water with glucose is perfused through the peritoneal cavity, the muscular symptoms soon develop, and the effect is ordinarily fatal in from two to five hours, on an average in about three hours. Howeveŗ, by supplying adequate sodium chloride intravenously by this method, it was possible to keep one animal alive 17½ hours—five times as long as during the perfusion of distilled water alone. During the experiment there was an occasional mild muscular fibrillation. There were no severe tremors or no convulsions. A marked diuresis oc-

TABLE 1

	Blood before perfusion Mg. per 100 cc.	Blood at end of experiment Mg. per 100 cc.
NaCl	463	402
N. P. N.	37.5	40
Urea	14	21
Sugar	138	163
Plasma CO_2 capacity	45 cc. per 100 cc. plasma	22 cc. per 100 cc. plasma
Plasma NaCl	592	• 750
Serum Calcium	9.3	3.8

curred, lasting about 12½ hours, but decreasing during the last five hours until the urinary secretion was slightly less than normal at the end of the experiment. There was a slight fall in the whole blood chloride, however, no hypochloremia as in the water-alone experiments. The plasma chloride was high. There was no tetany, although the serum calcium fell to 3.8 milligrams per 100 cubic centimeters. A definite hemolysis was present.

BLOOD CHEMISTRY CHANGES

The changes in the blood chemistry are best presented in Table 1.

Rabbit 2.5 kilograms. *Perfusion fluid,* distilled water with 0.12 per cent glucose; *Rate,* 500 cubic centimeters per hour. Simultaneous *intravenous injection* of 2.5 per cent pure sodium chloride at the rate of 1 cubic centimeter per minute. *Duration* 17½ hours.

In a subsequent experiment, the combined intravenous infusion and transperitoneal perfusion were similarly maintained for twelve hours without the development of symptoms. At the end of that time the intravenous injection of sodium chloride was stopped, but the perfusion of distilled water with glucose continued. Muscular twitchings then developed and became more severe; finally convulsions ensued and death followed after five hours of perfusion alone. In another experiment the simultaneous intravenous administration of Ringer's solution *without the sodium chloride* did not prevent the development of symptoms nor the lethal effect, and this animal died 5½ hours after the perfusion began.

SUMMARY

These experiments represent a study of certain of the effects of peritoneal dialysis, particularly in the production of experimental hypochloremia. It is difficult properly to evaluate, with the data at hand, the complex physico-chemical changes which result in the blood and tissues of the dialyzed animals. However, the experiments demonstrate the importance of sodium chloride to life and a state of well-being. In addition, from them may be deduced a rational explanation of the anuria accompanying the hypochloremia of intestinal obstruction.

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ASPIRATION IN TONSILLECTOMY—COMPARATIVE MERITS OF POSTURE AND OTHER FACTORS*

A BRONCHOSCOPIC STUDY OF ONE HUNDRED AND TEN PATIENTS

Research Prize Paper of the Fifty-Ninth Annual Session of the California Medical Association

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ONE-THIRD of all the surgical operations since 1924 among the American urban population are said to have been for the removal of tonsils and adenoids.[1] With the apparent increase of incidence of postoperative pulmonary complications, the problem of ascertaining the factors that might lead to the production of lung abscess merits earnest consideration.

In recent years much light has been shed on the etiology of postoperative complications. Concerning their causation, investigators in this field are now divided into two schools of thought: those who hold to the embolic, and those who defend the aspiration theories. That infecting emboli play a distinct part in some cases of lung abscess is well supported by both clinical and experimental evidences as shown by Cutler and Hunt,[2] Schlueter and Werdlein,[3] Fetterolf and

Fox,[4] and many others. It is also true that under certain circumstances, the aspiration of infected material into the air passages contributes to the causation of lung abscess, a fact which is demonstrated by the works of Hoelscher,[5] Lemon,[6] Smith,[7] Crowe and Scarff,[8] Allen,[9] Ochsner and Nesbit,[10] Myerson,[11] Iglauer,[12] and recently by May and his associates.[13] A careful review of recent literature on this subject impresses one with the fact that the pendulum of medical thought is swaying toward the side of the aspiration theory.

INCIDENCE

The first lung abscess following tonsillectomy in this country was reported in 1912 by Richardson.[14] Moore[15] estimated the incidence of lung abscess as once in 2500 to 3000 posttonsillectomies. That rate was based on a nation-wide survey by means of comprehensive questionnaires sent out to various throat specialists. Moore thus assembled 202 cases of lung abscess most of which followed tonsillectomy, thirty-nine of the tonsillectomies having been done under local anesthesia. Cutler and Schlueter[16] collected from the literature a total of 1908 cases of pulmonary abscess; 29 per cent of these followed operative procedures, and of such 14.6 per cent occurred after the removal of tonsils. In a series of 602 cases of pulmonary abscess which were observed at the Mayo Clinic by Hedblom,[17] 146 followed operations. Of these operative cases, forty-eight occurred after tonsillectomy.

From the records at the Massachusetts General Hospital the writer collected sixty cases of pulmonary complications which were recorded in the period between May 1921 and October 1927. This series included forty-five lung abscesses, eight lobar pneumonias, four cases of bronchiectasis, and three cases of bronchopneumonia. All followed operations on the upper respiratory tract, chiefly on tonsils and adenoids under inhalation ether anesthesia. Of these sixty patients, thirty-nine were operated on elsewhere than at the Massachusetts General Hospital. When the complications later developed, the patients sought medical aid in the above hospital. The remaining twenty-one cases included two bronchopneumonias, eight lobar pneumonias, and eleven lung abscesses. These patients had been operated on either at the Massachusetts General Hospital or at the Massachusetts Charitable Eye and Ear Infirmary, these two institutions being under the same management. During this same period the average number of tonsillectomies performed each year in these two institutions was 3356. This places the actual known incidence of lung abscess in these two institutions as one in every 2678 tonsillectomies.

SCOPE OF EXPERIMENT

By means of bronchoscopic studies Myerson[10] and Iglauer[11] have shown that 40 to 77.5 per cent of patients, immediately following tonsillectomy under ether anesthesia, revealed the presence of blood and mucus in some portion of the bronchial tree. Iglauer reported that when tonsils were removed under local anesthesia, aspiration